THE CONTROL OF HYPERTENSION AMONG PATIENTS ATTENDING HOSPITAL UNIVERSITI SAINS MALAYSIA'S HYPERTENSION CLINIC

BY

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List of abbreviations

ACC	: American College of Cardiology
ACE	: Angiotensin converting enzyme
AHA	: American Heart Association
ALLHAT	: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	: Angiotensin receptor blocker
ASCOT-BPLA	: Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm
BB	: Beta blocker
BP	: Blood pressure
CCB	: Calcium channel blocker
CI	: Confidence interval
CHD	: Coronary heart disease
CKD	: Chronic kidney disease
CVD	: Cardiovascular disease
DBP	: Diastolic blood pressure
eGFR	: Estimated glomerular filtration rate
ESC	: European Society of Cardiology
ESH	: European Society of Hypertension
FBS	: Fasting blood sugar
HDL-C	: High density lipoprotein - cholesterol
HF	: Heart failure

HOPE	: Heart Outcomes Prevention Evaluation
HOT	: Hypertension Optimal Treatment
ISH	: International Society of Hpertension
JNC	: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL-C	: Low density lipoprotein – cholesterol
MDRD	: Modification of Diet in Renal Disease
n	: Number
OR	: Odds ratio
SBP	: Systolic blood pressure
SD	: Standard deviation
SE	: Standard error
TOD	: Target organ damage
WHO	: World Health Organisation

Abstrak

Latarbelakang Darah tinggi merupakan satu masalah perubatan yang kerap berlaku dan ianya berkait dengan penyakit jantung koronari, angina ahmar, lemah jantung dan kegagalan ginjal. Masih ramai pesakit darah tinggi yang mempunyai tekanan darah yang tidak dikawal walaupun menerima rawatan dengan ubat anti-darah tinggi.

Tujuan Kajian ini dilakukan dengan objektif utama untuk menilai peratusan pesakit yang berjaya mencapai tahap tekanan darah terkawal. Objektif kedua adalah untuk menyelidik factor-faktor yang berkait dengan tekanan darah yang tidak terkawal dan menilai jumlah ubat anti-darah tinggi yang diperlukan untuk mengawal tekanan darah.

Kaedah Kajian secara keratan lintang (*cross sectional*) dilakukan di kalangan pesakit darah tinggi yang menerima rawatan di klinik darah tinggi Hospital USM dari April hingga September 2006. Tekanan darah pesakit, sejarah merokok, jisim berat badan, ujian protein didalam air kencing, profil kolesterol semasa puasa, profil ginjal dan tahap gula semasa puasa diambil. Tahap tekanan darah terkawal adalah < 140/90 mmHg atau < 130/80 mmHg jika pesakit mengidap kencing manis atau kegagalan ginjal kronik, atau < 125/75 mmHg jika pesakit mempunyai protein didalam air kencing > 1g sehari.

Keputusan Seramai 245 pesakit yang telah mengambil ubat mengikut saranan doktor menyertai kajian ini. Tiga puluh empat peratus pesakit berjaya mencapai tahap tekanan darah yang terkawa (n = 83). Pesakit yang mengalami kegagalan ginjal kronik merupakan

majoriti (69.14%) dikalangan pesakit yang mempunyai tahap tekanan darah tidak terkawal. Analisis univariat menunjukkan bahawa beberapa factor berkait dengan tekanan darah tidak terkawal iaitu: peningkatan umur, bangsa melayu, sejarah merokok; peningkatan kadar kreatinin, asid urik, jumlah kolesterol, trigliserid dan gula semasa puasa; penurunan eGFR; penggunaan ubat anti-darah tinggi melebihi 2 jenis dan penggunaan ubat diuretik; pesakit yang mempunyai kencing manis, kegagalan ginjal kronik dan protein didalam air kencing. Walaubagaimanapun analisis menggunakan kaedah regresi logistik berbilang (*multiple logistic regression*) menunjukkan pesakit wanita ($p = 0.001$), bangsa melayu ($p = 0.031$), merokok ($p < 0.001$), eGFR ($p < 0.001$) dan penyakit kencing manis ($p = 0.001$) merupakan faktor-faktor tak bersandar yang berkait dengan tahap darah tinggi tidak terkawal. Pesakit yang menerima rawatan dengan 1 atau 2 ubat anti-darah tinggi mempunyai peluang yang lebih tinggi untuk mencapai tahap tekanan darah terkawal berbanding pesakit yang menerima rawatan dengan lebih dari 2 ubat mengikut analisis univariat, tetapi keputusan ini tidak ketara secara statistik melalui analisis multivariat.

Kesimpulan Majoriti pesakit darah tinggi tidak mencapai tahap tekanan darah terkawal. Faktor-faktor berasingan yang berkait dengan tekanan darah tidak terkawal adalah kaum wanita, bangsa melayu, merokok, eGFR dan penyakit kencing manis. Kegagalan ginjal kronik menjadi penyumbang utama kepada masalah tekanan darah tinggi tidak terkawal. Perawatan penyakit darah tinggi yang lebih intensif diperlukan untuk meningkatkan peratusan pesakit yang mencapai tahap tekanan darah terkawal dan mengurangkan komplikasi akibat darah tinggi.

Abstract

Background Hypertension is a common medical problem and it is associated with coronary artery disease, stroke, heart failure and renal dysfunction. However many patients still have an uncontrolled blood pressure despite antihypertensive treatment.

Objectives This study was conducted with the primary objective of assessing the proportion of patients who achieved their blood pressure targets. The secondary objectives were to evaluate the factors associated with uncontrolled blood pressure and to determine the number of antihypertensive agents required to achieve controlled blood pressure.

Methods A cross-sectional study of hypertensive patients attending Hospital USM hypertension clinic was conducted from April until September 2006. Patients' blood pressure, smoking history, BMI, urinalysis for protein, fasting lipid profile, renal function test and fasting blood sugar were obtained. The blood pressure was defined as controlled if < 140/90 mmHg or < 130/80 mmHg in patients with diabetes or chronic kidney disease, or < 125/75 mmHg in patients with proteinuria > 1g/day.

Results A total of 245 patients compliant to medications were recruited. Thirty four percent of them achieved controlled blood pressure (n = 83). Patients with chronic kidney disease were the majority (69.14%) among patients with uncontrolled blood pressure. Univariate analysis showed several factors were associated with uncontrolled blood pressure: older age, malay race, history of smoking; higher creatinine, uric acid,

total cholesterol, triglyceride and fasting blood sugar; lower eGFR; the use of more than 2 antihypertensive agents and the use of diuretics; and the presence of diabetes mellitus, chronic kidney disease and proteinuria. However the results of multiple logistic regression analysis indicated that female gender ($p = 0.001$), malay race ($p = 0.031$), smoking ($p < 0.001$), eGFR ($p < 0.001$) and diabetes mellitus ($p = 0.001$) were the independent factors associated with uncontrolled blood pressure. Univariate analysis showed that patients who were on treatment with 1 or 2 antihypertensive agents were more likely to have controlled blood pressure than those on more than 2 drugs ($p = 0.001$), however, this was not statistically significant in multivariate analysis.

Conclusions Majority of the hypertensive patients failed to achieve their blood pressure targets. The independent factors associated with uncontrolled blood pressure in our hypertensive population were female gender, malay race, smoking, eGFR and diabetes mellitus. Patients with chronic kidney disease contributed to a considerable number of patients with uncontrolled blood pressure. More intensive management of hypertension is needed to increase the proportion of patients with controlled blood pressure and to reduce the complications of hypertension.

Chapter 1

1.0 Introduction

Hypertension is one of the major health burdens in many countries. It is the most preventable cause of premature death in the developed countries (Ezzati et al, 2002). In the World Health Organisation Report 2002 it has been estimated that the worldwide prevalence of hypertension was approximately 1 billion and 7.1 million deaths per year could be related to hypertension (World Health Report, 2002). Data from the cross sectional analysis of adults surveyed in the 1999-2000 National Health and Nutrition Examination Survey in the United States revealed that 60% of American adults have pre-hypertension or hypertension (Wang QJ and Wang Y, 2004). Approximately 30% of Americans with hypertension were unaware of their hypertension. The data also revealed that more than 40% of hypertensive individuals were not on treatment and two-thirds of patients with hypertension did not achieve target blood pressure < 140/90 mmHg. In Malaysia, data from the First National Health and Morbidity Survey 1988 found that the percentage of adults with hypertension in Peninsular Malaysia was 14.4% (NCD Malaysia, 2002). The results of a second survey in Malaysia, The National Health and Morbidity Survey 1996, however showed that 33% of Malaysian adults had hypertension. Only 33% of individuals were aware of their hypertension with 23% were currently on treatment and only 6% had controlled hypertension (Lim and Morad, 2004). Data from surveys carried out in 1990s in 5 European countries (Germany, Sweden, Spain, England, Italy), Canada and United States demonstrated different control rates among these regions. It showed the percentage of hypertensive individuals with blood pressure control

at < 140/90 mmHg was 29% in United States, 19% in Canada and ≤10% in the European countries (Wolf-Maier et al, 2004).

Epidemiological studies have identified an important association between hypertension and coronary artery disease, stroke, congestive heart failure and renal insufficiency. The relationship between blood pressure and risks of cardiovascular events is continuous. Death from ischaemic heart disease and stroke increases in a linear progression from systolic blood pressure 115 mmHg and diastolic blood pressure 75 mmHg upward. The mortality from ischaemic heart disease and cerebrovascular disease among individuals aged 40 to 70 years doubles for every 20 mmHg systolic and 10 mmHg diastolic increase in blood pressure (Lewington et al, 2002). In the World Health Organisation Report 2002, suboptimal BP was responsible for 62% of cerebrovascular disease and 49% of ischaemic heart disease (World Health Report, 2002). Data from the Framingham Heart Study revealed that there was more than twofold rise in relative risk of cardiovascular event for those individuals with blood pressure between 130-139/85-89 mmHg compared to those with blood pressure below 120/80 mmHg (Vasan et al, 2001). It has been estimated that reduction of systolic blood pressure by 5 mmHg in the population would result in 14% reduction in mortality due to stroke, 9% reduction in mortality due to coronary heart disease and 7% reduction in all-cause mortality (Stamler et al, 1991 and Whelton et al, 2002). In Malaysia, cardiovascular disease (CVD) was a principal cause of death in government hospital (15.8%), followed by malignant neoplasm (9.34%) and cerebrovascular accident (9.27%) (Kementerian Kesihatan Malaysia, 2000). Hospitalisation due to CVD in government hospitals in Malaysia

showed an increasing trend with 78 800 cases in 1990 and 108 087 in 2000, an increase of 37.2%. Hospitalisation due to hypertension also showed a similar trend with an increased of 22.3% from 1999 to 2000.

The use of antihypertensive therapy has been associated with 30-45% reduction in incidence of stroke, 20-25% reduction in myocardial infarction and more than 50% in heart failure (Neal et al, 2000). Majority of hypertensive patients require two or more anti-hypertensive agents to control the blood pressure (Hansson et al, 1998). In The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 60% of participants whose blood pressure was controlled received two or more agents (Cushman et al, 2002). Thiazide-type diuretic has been used in several placebo-controlled studies which showed reduction of stroke, coronary heart disease and heart failure by blood pressure reduction (Cutler et al, 1989 and Psaty et al, 1997). The use of other classes of drugs including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs) and calcium channel blockers (CCBs) in lowering blood pressure have also been shown to reduce the complications of hypertension. The Medical Research Council Trial of middle aged hypertensive subjects found no overall difference in outcome between a thiazide diuretic and propranolol, both of which were more effective than placebo (MRC Trial, 1985). In the STOP-hypertension-2 trial, elderly hypertensive patients (age 70-84 years) were randomized to one of three groups: conventional treatment with beta blocker or diuretic; an ACE-inhibitor (enalapril or lisinopril); or a dihydropyridine calcium channel blocker (felodipine or isradipine). The results showed the degree of blood pressure control, the

combined endpoint of fatal and nonfatal stroke or myocardial infarction and other cardiovascular mortality were similar in the 3 groups (Hansson et al, 1999). Data from the United Kingdom Prospective Diabetes Study (UKPDS) revealed that atenolol was as effective as captopril in terms of blood pressure lowering and protection against microvascular disease among patients with Type 2 diabetes who were not selected for being at increased risk of cardiovascular disease (UKPDS Group, 1998).

In the Heart Outcomes Prevention Evaluation (HOPE) study which also included hypertensive subgroup, ramipril has been shown to reduce cardiovascular events in individuals with prior cardiovascular disease or diabetes mellitus combined with other risk factor(s) (Yusuf et al, 2000). Perindopril was used in European Trial on Reduction of Cardiac Events (EUROPA) study in stable coronary artery disease which also showed reduction in cardiovascular events (Fox et al, 2003). An angiotensin receptor blocker losartan was investigated in Losartan Intervention for Endpoint Reduction in Hypertension study (LIFE), in which losartan was associated with significant reduction in composite endpoint of cardiovascular death, myocardial infarction or stroke compared with atenolol (Dahlof et al, 2002).

The new classes of antihypertensive agents, including calcium-channel blockers, angiotensin converting enzyme inhibitors, and alpha adrenergic blockers, became available for chronic hypertension management in the 1970s and 1980s. Placebo-controlled trials documented the ability of ACEI and CCB to reduce cardiovascular events, but there was limited evidence of their performance compared with older, less

expensive agents (Davies et al, 1996). In The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) patients were randomized in a double-blind trial designed to determine whether the incidence of cardiovascular endpoints differs between diuretic (chlorthalidone) treated patients and those treated with a CCB (amlodipine), an ACEI (lisinopril), or an alpha blocker (doxazosin) (Cushman et al, 2002). The alpha blocker arm was terminated early because of increased risk of secondary endpoint of combined cardiovascular disease. There was no significance difference observed between the amlodipine and chlorthalidone arm, or between lisinopril and chlorthalidone arms for the primary outcome of fatal and non-fatal coronary disease. In the recent Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA) which compared the treatment with CCB (amlodipine) based treatment against beta-blocker (atenolol) based treatment, the amlodipine-based treatment was shown to be better than atenolol-based treatment in terms of reducing the incidence of all types of cardiovascular event and all-cause mortality (Dahlof et al, 2005).

1.1 Definition and classification of hypertension

The continuous relationship between the level of blood pressure and cardiovascular risk makes any numerical definition and classification of hypertension arbitrary. The definition of hypertension by Rose (Evans and Rose, 1971) more than 30 years ago which stated 'Hypertension should be defined in terms of a blood pressure level above which investigation and treatment do more good than harm' indicates that any numerical definition must be a flexible one. It would therefore be appropriate to use a classification of blood pressure without the term 'hypertension' (ESH-ESC, 2003).

Hypertension has been defined by the International Society of Hypertension/World Health Organisation (ISH/WHO) as a SBP of 140 mmHg or greater and/or a DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication (ISH/WHO, 1999). The classification as suggested by the ISH/WHO is shown in table 1.1 . The European Society of Hypertension has adopted the 1999 World Health Organisation/International Society of Hypertension (WHO/ ISH) classification with some modifications. It emphasizes reservation that the real threshold for hypertension must be considered as flexible, being higher or lower based on the total cardiovascular risk profile of each individual (European Society of Hypertension Committee, 2003). Accordingly, the European Society of Hypertension definition of high normal blood pressure (Table 1.2) includes values that may be considered as 'high' (i.e. hypertension) in high-risk subjects, or acceptable in individuals at lower risk.

In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7, 2003) a new category designated as prehypertension has been used whereas hypertension stages 2 and 3 have been combined. The new category of prehypertension for those with BP ranging from 120-139 mmHg systolic and / or 80-89 mmHg diastolic has been introduced as new data on lifetime risk of hypertension and also increase risk of cardiovascular complications have been associated with blood pressure previously considered to be normal. Prehypertension is not a disease category. This new designation is intended to identify those individuals in whom early intervention by adoption of healthy lifestyles could

reduce blood pressure, decrease the rate of progression of blood pressure to hypertensive levels with age, or prevent hypertension entirely. Individuals who are prehypertensive are not candidates for drug therapy based on their level of blood pressure and should be advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future. Moreover, individuals with prehypertension who have diabetes or kidney disease, should be considered candidates for appropriate drug therapy if a trial of lifestyle modification fails to reduce their BP to <130/80 mmHg. The classification of blood pressure according to JNC 7 and also the previous classification from JNC 6 are shown in table 1.3.

Table 1.1 Definitions and classification of blood pressure levels (ISH/WHO)

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	<130	<85
High Normal	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
Subgroup: borderline	140-149	90-94
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: borderline	140-149	<90

Adapted from 1999 World Health Organisation / International Society of Hypertension (ISH/WHO) Guidelines for management of hypertension, Journal of Hypertension (1999)

Table 1.2 Definitions and classification of blood pressure levels (ESH-ESC)

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
High Normal	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

Adapted from 2003 European Society of Hypertension-European Society of Cardiology (ESC-ESH) guidelines for management of arterial hypertension, Journal of Hypertension (2003)

Table 1.3 Changes in Blood Pressure Category

JNC 6 category		JNC 7 category
	SBP/DBP	
Optimal	<120/80	→ Normal
Normal	120-129/80-84	Prehypertension
Borderline	130-139/85-89	
Hypertension	≥140/90	→ Hypertension
Stage 1	140-159/90-99	→ Stage 1
Stage 2	160-169/100-109	Stage 2
Stage 3	≥180/110	

Adapted from Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2003)

1.2 Assessment of risk

The management of hypertension should not emphasis on achieving target blood pressure levels only but also needs to assess the presence of other cardiovascular risk factors, target organ damage, and associated clinical conditions. There are many factors which influence the prognosis of patients with hypertension. Factors which are associated with increased risk of cardiovascular disease include levels of systolic and diastolic blood pressure, male >55 years, female >65 years, smoking, total cholesterol more than 6.5mmol/l, LDL-cholesterol more than 4mmol/l, HDL-cholesterol (less than 1mmol/l in males, less than 1.2mmol/l in females), family history of premature cardiovascular disease in the first degree relatives and abdominal obesity (Table 1.4). In the assessment of hypertension we should also look for the presence of target organ damage such left ventricular hypertrophy, retinopathy, microalbuminuria; establish other associated clinical conditions such as cerebrovascular disease, heart disease, renal disease and peripheral vascular disease and also assess for the presence of diabetes mellitus (Table 1.4).